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Phytochemical Mimicry of Reproductive Hormones and Modulation of Herbivore Fertility by Phytoestrogens

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Plants have physical and chemical mechanisms for defense from attack by animals. Phytochemical defenses that protect plants from attack by insects include antifeedants, insecticides, and insect growth regulators. Phytochemical options exist by which plants can modulate the fertility of the other major group of plant predators, vertebrate herbivores, and thereby reduce cumulative attacks by those herbivores. The success of such a defense depends upon phytochemical mimicry of vertebrate reproductive hormones. Phytoestrogens do mimic reproductive hormones and are proposed to be defensive substances produced by plants to modulate the fertility of herbivores.

Introduction to Plant Defensive Options

Survival of all higher animals depends directly or indirectly upon predation on plants. In turn, defense mechanisms have evolved by which plants modulate the degree of predation by animals. Obvious mechanisms of plant defense include physical repulsion of attack by cuticle, spines, thorns, etc. Phytochemical options for defense from animal predation include repulsion due to aversive odors or tastes, toxicity *per se,* including lethality to the individual, or fertility regulation.

A substantial body of data exists that illustrates the chemical defenses used by plants to reduce predation by insects. Reviews by Bowers (*1*) and Nakanishi (*2*) summarize the occurrence and effects of phytochemicals as insect antifeedants, insecticides, and insect growth regulators. The subtle efficacy of the insect growth regulators depends upon predation of the plant by the attacking insect, but in turn, the growth and/or reproductive maturation of the insect is disordered, typically producing sterility in that individual insect. The short-term predatory cost to the plant is more than compensated by the obvious long-term benefit of a reduction in the population of insect predators (of that species) in that vicinity in the future. The fertility of the other major group of plant predators, vertebrate herbivores, is also subject to modulation by phytochemicals.

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Expectations for the General Case of Phytochemical Modulation of Herbivore Fertility

If phytochemical modulation of herbivore fertility does indeed exists, then general requirements, expectations, or predictions can be formulated for the source plants and target animals. Some of the expected properties of such a system would include the following:

a) A chemical or groups of chemicals found in plants must exist that adversely affect herbivore reproduction.

b) Such phytochemical reproductive inhibitors would be luxury molecules in that substances synthesized for defensive purposes would not be expected to serve as an integral structural of functional entity in the source plant.

c) Because plants cannot escape attack by moving elsewhere and many plants occur as patchy food sources, inhibition of herbivore reproduction in the same locale would reduce herbivore numbers and thus cumulatively reduce the degree of predation on the plant or its genetically similar cohort or progeny.

d) While phytochemical defenses involving general growth regulators or neurotoxins may be efficacious, reproductive specificity of defensive phytochemicals would be most readily attained by mimicry of reproductive hormones.

e) As a corollary to item *d*, hormonal agonism or antagonism would both be effective pertubations of reproduction.

f) Some convergence in evolution of diverse plant species in the development of phytochemicals that modulate herbivore reproduction would be anticipated if this general defensive strategy is efficacious.

g) The precise mechanism or point of action of the phytochemical in the herbivore must be a fundamental component in reproduction.

h) There should be universality of the mechanism that is compromised by the phytochemical. The efficiency of the plant's defense is greatly increased if a single chemical (or group of chemicals) is effective against various herbivore species.

i) The female herbivore shoud be the primary target of phytochemical action. "Since the adult females are committed to an expenditure of substantial amount of time and energy, they are the limiting resources. . . " (*3*). While phytochemical pertubation of reproductive function of male herbivores could benefit the plant, persistence of even a few fertile males in the population may yield no change in the fecundity or prolificacy of the population. For many species (i.e., rodents, lagamorphs, ruminants, etc.) biological or behavioral constraints do not exist that would preclude impregnation of many females by a single male.

j) Multiple sites of action of the phytochemical would magnify the efficacy of that agent if several components of herbivore reproduction were adversely affected at once. Alternatively, the interval of susceptibility to pertubation of reproduction could be greatly increased if several different steps in reproduction were subject to disturbance by the phytochemical.

k) As modulation of herbivore reproduction requires some ingestion of the source plant, delivery of the phytochemical may be subtle. Immediate detection by the ingesting animal might compromise the strategy. If moderate ingestion of the plant by an individual herbivore prevents litters of offspring later, the modest cost to the plant permitting limited ingestion may be greatly compensated in the long run by reduced attacks on the plant or its progeny, especially if seeds would be destroyed or if younger plants commonly die after an attack.

Phytoestrogens as Modulators of Herbivore Fertility

Phytoestrogens fulfill the requirements and expectations delineated for the general case of modulation of herbivore fertility by phytochemical mimicry of reproductive hormones. Estrogens (especially estradiol-17β) are critical and fundamental to vertebrate reproduction and requirement for estrogens in female reproductive physiology is persuasively universal. Some general examples include the following:

Early exposure to sex steriods permanently alters the sexual behavior of fish, amphibians, reptiles, birds, and mammals (*4*), although the role of sex steroids in the differentiation of gonads and gonaducts does appear to vary among classes of vertebrates.

In adult female mammals of many different species, it is proven that estrous (mating) behavior is critically dependent upon estrogen production/exposure (*5*). Additionally, at least in the rat, such a response may be subsequently augmented by progestins.

An obligatory antecedent rise in plasma estradiol produces an ovulatory surge of luteinizing hormone in spontaneously ovulating mammals such as rodents, ruminants, canines, and primates, whereas reflex ovulating mammals such as felines and lagamorphs have essentially continuous estrogen production from overlapping waves of maturing ovarian follicles (*5*).

Over 300 plants in more than 16 different families contain substances with estrogenic activity (*6*). Table 1 summarizes the occurrence of phytoestrogens in some

Table 1. Occurrence and content of phytoestrogens in common plants.[a]

	Plants		
Family	Examples	Phytoestrogens	Estimates of content
Chenopodiaceae	Beet	Unidentified	+[b]
Compositae	Sunflower	Coumestans[c]	+
Cruciferae	Rape	Unidentified	+
Euphorbiaceae	Caster oil plant	Unidentified	+
Gramineae	Barley Bluegrass Oats Orchardgrass Rye Ryegrass Rice Wheat	Isoflavonoids,[d] coumestans, and resorcylic acid lactones	+ to +++
Labiatae	Sage	Unidentified	++
Leguminosae	Alfalfa Clovers (red, strawberry, subterraneum, and others) Soybean	Isoflavonoids and coumestans	++[e]
Liliaceae	Garlic	Unidentified	+++
Malvaceae	Hollyhock	Unidentified	+
Palmaceae	Date palm	Unidentified	+
Polygonaceae	Rubarb	Unidentified	+
Rosaceae	Apple Cherry Plum	Unidentified	+
Rubiaceae	Coffee	Unidentified	+
Salicaceae	Willow	Unidentified	++
Solanaceae	Potato	Unidentified	+
Umbelliferae	Parsley	Unidentified	+

[a]Adapted from Bradbury and White (*7*) and Farnsworth et al. (*6*).
[b]Summary of available bioassay studies: + = weakly estrogenic; ++ = moderately estrogenic; +++ = strongly estrogenic.
[c]Coumestans include coumestrol and related compounds.
[d]Isoflavonoids include genistein, daidzein, formononetin, Biochanin A, and related compounds.
[e]Up to 1% of the dry weight of some clovers may be isoflavonoids (*8*). Soybean products contain 2.2–48.0 mg daidzein/100 g, 11–114 mg daidzin/100 g, 4–108 mg genistein/100 g, and 81.3–215 mg genistin/100 g [summarized in Setchell (*23*)].

common plants. Estimates of content primarily represent bioassay studies by many different workers over the last four decades. The phytoestrogens that have been isolated, purified, and identified are primarily isoflavonoids and coumestans. These classes of compounds are widely present in the Gramineae and Leguminosae families which include many grain crops and livestock forages. Such agricultural plants have been preferentially studied because the phytoestrogen content is high (Table 1); reproductive failure in livestock was the first evidence that such substances exist, and the financial consequences of infertility in livestock are obvious.

The classic scenario of adverse effects to herbivore fertility from the ingestion of phytoestrogen-containing plants is clover disease in sheep in Western Australia. Prolonged ingestion of some varieties of subterranean clover that contain estrogenic isoflavones (*15*) can cause permanent infertility in sheep (*16*), such that animals grazing on such pasture in preparation for experimental studies have an overall lambing rate of less than 10% per annum (*17*). Other studies suggest that exposure to such estrogenic pastures can compromise fertility in sheep by interference with sperm transport (*18,19*) and fertilization and early embryonic loss (*19,20*). Alterations in estrous cycle physiology have been demonstrated in exposed sheep (*21*). The hypothalamic positive feedback of estradiol-17β to provoke a midcycle surge of luteinizing hormone and thus ovulation is compromised in sheep grazed on such pastures (*17*). This well-studied example of effects of phytoestrogens on reproduction of one herbivore therefore illustrates several of the expectations for the general case, including adverse effects on herbivore reproduction with diminution of fertility and thus herbivore numbers, a multiplicity of sites of action, and a primarily female herbivore target. The sheep will readily graze the estrogenic clover for years, so immediate detection and thus aversion does not occur.

Data from several different sources indicate that phytoestrogen-induced infertility in sheep is not unique to that herbivore. Animals as diverse as cattle, mice, and quail have been shown to suffer reproductive failure due to dietary phytoestrogens (Table 2). Livestock and laboratory species have been studied most extensively, but field biology studies in many wild herbivore species are lacking.

The amounts of phytoestrogens in the diets of animals shown to suffer reproductive compromise are shown in Table 2. In general, these data represent endogenous phytoestrogen content rather than spiking other dietary constituents with purified compounds. Investigations are needed that include concurrent quantitation of dietary phytoestrogens, reproductive outcome, and physiological parameters of herbivore reproduction.

The notion that phytoestrogens are chemical products of plants that do not serve an essential intrinsic function but are luxury molecules dedicated to defense is probable but not proven. Alternative proposals for the functional roles of estrogenic substances within plants include flower pigment production or lignification, but a comprehensive review by Stob (*9*) failed to show any convincing data to support such nondefensive roles.

The specificity of hormonal mimicry by various phytoestrogens has been extensively studied (*22,23*). The various groups of phytoestrogens, including isoflavones, coumestans, and resorcylic acid lactones, as well as estradiol-17β and estrone, have been shown to bind to estrogen receptors, effect the changes described as nuclear translocation, and to manifest tissue effects consistent with estrogenic activity. Alternative antiestrogenic effects of phytoestrogens have been described in mice, and the relative agonistic or antagonistic actions of such compounds may depend upon the dose ingested (*24,25*).

The existence of more than 20 phytoestrogens of 4 chemically distinct classes with demonstrable receptor specificity in more than 300 different plants can be taken to imply convergence in the evolution of plant defensive strategies. Any plant defensive strategy short of immediate herbivore death following ingestion of the plant allows that herbivory may not be exclusively detrimental to the plant. While there clearly are indirect benefits of herbivory such as predation of competing plants and seed dispersal, the possibility that

Table 2. Demonstrated reproductive effects of dietary phytoestrogens.[a]

Herbivore	Reproductive effects	Dietary composition	Estimate of phytoestrogen intake
Bos taurus (cattle)	Infertility (*10*)	Alfalfa	14–135 ppm coumestro (*11*)
Cavia porcellus (guinea pigs)	Infertility (*10*)	Subterranean clover	0.4–1.0% w/w isoflavonoids (*8*) and coumestans
Lophortyx californicus (California quail)	Inhibition of reproduction (*12*)	Forbs	Semi-quantitative estimates of isoflavonoids; varied with growth conditions (*12*)
Mus musculus (mice)	Infertility, inhibition of estrus, inhibition of ovulation (*13*)	15–30% Ladino clover in diet	Isoflavonoids; content estimated by bioassay only (*13*)
Oryctolagus cuniculus (rabbits)	Infertility, failure of ovulation, failure of implantation (*14*)	Ladino clover or Ladino hay	Isoflavonoids; content estimated by bioassay only (*14*)
Ovis aries (sheep)	Infertility, dystocia, sterility	Subterranean clover	0.4–1.0% w/w isoflavonoids (*8*) and coumestans

[a]Adapted from Stob (*9*).

herbivory directly increases the fitness of plants remains controversial. In a recent thorough review, Belsky (*26*) concluded that the available evidence did not substantiate the notion that the fitness of plants was increased by herbivory. An even more recent study of a montane herb (scarlet gilia) clearly demonstrated a beneficial effect of browsing due to a consequent marked increase in production of fertile seeds (*27*).

Massive bodies of data exist that demonstrate that specific phytochemicals regulate insect reproduction. The present report demonstrates that phytoestrogens are capable of profoundly affecting herbivore reproduction. Phytoestrogens may thus be defense substances produced by many plants to modulate the fertility and therefore the population of herbivores that ingest portions of such a plant or its genetically similar cohort. The cumulative long-term benefit to the plant or its progeny is decreased predation by herbivores.

REFERENCES

1. Bowers, W. S. Chemistry of plant/insect interactions. In: Insect Biology in the Future (M. Locke and D. S. Smith, Eds.), Academic Press, New York, 1980, pp. 613–633.
2. Nakanishi, K. Insect antifeedants from plants. In: Insect Biology in the Future (M. Locke and D. S. Smith, Eds.), Academic Press, New York, 1980, pp. 603–611.
3. Wilson, E. O. Sociobiology: The New Synthesis. Belknap Press of Harvard University Press, Cambridge, MA, 1975, p. 456.
4. Adkins-Regan, E. Early organizational effects of hormones. In: Neuroendocrinology of Reproduction: Physiology and Behavior (N. T. Alder, Ed.), Plenum Press, New York, 1981, pp. 159–228.
5. Feder, H. H. Estrous cyclicity in mammals. In: Neuroendocrinology of Reproduction: Physiology and Behavior (N. T. Alder, Ed.), Plenum Press, New York, 1981, pp. 279–348.
6. Farnsworth, N. R., Bingel, A. S., Cordell, G. S., Crane, F. A., and Fond, H. H. S. Potential value of plants as sources of new antifertility agents II. J. Pharm. Sci. 64: 717–754 (1975).
7. Bradbury, R. B., and White, D. E. Estrogens and related substances in plants. In: Vitamins and Hormones, Vol. 12 (R. S. Harris, G. F. Marrian, and K. V. Thimann, Eds.), Academic Press, New York, 1954, pp. 207–230.
8. Wong, E. Isoflavone contents of red and subterranean clovers. J. Sci. Fd. Agric. 14: 376–379 (1963).
9. Stob, M. Naturally occurring food toxicants: Estrogens. In: Handbook of Naturally Occurring Food Toxicants (M. Rechcigl, Ed.), CRC Press, Boca Raton, FL, 1983, pp. 81–100.
10. Moule, G. R., Braden, A. W. H., and Lamond, D. R. The significance of oestrogens in pasture plants in relation to animal production. Anim. Breeding Abstr. 31: 139–157 (1963).
11. Montgomery, G. W., Martin, G. B., LeBars, J., and Pelletier, J. Gonadotropin release in ovariectomized ewes fed different amounts of coumestrol. J. Reprod. Fertil. 73: 457–463 (1985).
12. Leopold, A. S., Erwin, M., Oh, J., and Browning, B. Phytoestrogens: Adverse effects on reproduction in California quail. Science 191: 98–99(1976).
13. Leavitt, W. W., and Wright, P. A. Effect of legumes on reproduction in mice. J. Reprod. Fertil. 6: 115–123(1963).
14. Wright, P. A. Infertility in rabbits induced by feeding ladino clover. Proc. Soc. Exp. Biol. Med. 105: 428–430(1960).
15. Braden, A. W. H., Hart, N. K., and Lamberton, J. A. The oestrogenic activity and metabolism of certain isoflavones in sheep. Aust. J. Agric. Res. 18: 335–348(1967).
16. Bennetts, H. W., Underwood, E. J., and Shier, F. L. A specific breeding problem of sheep on subterranean clover pastures in Western Australia. Aust. Vet. J. 22: 2–12(1946).
17. Findlay, J. K., Buckmaster, J. M., Chamley, W. A., Cummings, I. A., Hearnshaw, H., and Goding, J. R. Release of luteinizing hormone by oestradiol-17β and gonadotrophin-releasing hormone in ewes affected with clover disease. Neuroendocrinology 11: 57–66(1973).
18. Lightfoot, J. R., Croker, K. P., and Neil, H. G. Failure of sperm transport in relation to ewe infertility following prolonged grazing on oestrogenic pastures. Austr. J. Agric. Res. 18: 755–765 (1967).
19. Kaltenbach, C. C., and Davies, H. L. Fertilization, sperm transport, and early embryonic loss in ewes grazed on cultivars of subterranean clover (*T. subterraneum*). Aust. J. Agric. Res. 21: 107–114(1970).
20. Turnbull, K. E., Braden, A. W. H., and George, J. M. Fertilization and early embryonic losses in ewes that had grazed oestrogenic pasture for 6 years. Aust. J. Agric. Res. 17: 907–917(1966).
21. Hearnshaw, H., Brown, J. M., Cummings, I. A., Goding, J. R., and Nairn, M. Endocrinological and histopathological aspects of the infertility in the ewe caused by oestrogenic clover. J. Reprod. Fertil. 28: 160–161(1972).
22. Li, J. J., Li, S. A., Klicka, J. K., and Heller, J. A. Some biological and toxicological studies of various estrogen mycotoxins and phytoestrogens. In: Estrogens in the Environment (J. McLachlan, Ed.), Elsevier, New York, 1985, pp. 168–183.
23. Setchell, K. D. R. Naturally occurring non-steroidal estrogens of dietary origin. In: Estrogens in the Environment (J. McLachlan, Ed.), Elsevier, New York, 1985, pp. 69–85.
24. Leavitt, W. W., and Wright, P. A. The plant estrogen, coumestrol, as an agent affecting hypophysical gonadotropin function. J. Exp. Zool. 160: 319–327(1965).
25. Folman, Y., and Pope, G. S. The interaction in the immature mouse of potent estrogens with coumestrol, genistein and other uterovaginotrophic compounds of low potency. J. Endocrinol. 34: 215–225(1966).
26. Belsky, A. J. Does herbivory benefit plants? Am. Nat. 127: 870–891(1986).
27. Paige, K. N., and Whitman, T. G. Overcompensation in response to mammalian herbivory. Am. Nat. 129: 407–416(1987).